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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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11/25/2003

Jun Nakamura

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EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/720,177	<b>Applicant(s)</b> NAKAMURA ET AL.	
	<b>Examiner</b> Delia M. Ramirez	<b>Art Unit</b> 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 7/31/2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,4,5,8-16 and 18-21 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4,5,12-16 and 18-21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Application***

Claims 1, 4-5, 8-16, 18-21 are pending.

In view of the Examiner's inadvertent omission of claim 12 in the list of claims rejected under 35 USC 112, first paragraph, written description and scope of enablement, the finality of the Office action mailed on 10/16/2007 is hereby withdrawn. This action is identical in content to that mailed to Applicant on 10/16/2007 except that it includes claim 12 in the list of claims rejected under 35 USC 112, first paragraph.

Applicant's amendment of claims 1, 5, 13, 16, 19, addition of claims 20-21 and cancellation of claims 7, 17 as submitted in a communication filed on 7/31/2007 is acknowledged.

Applicant's submission of two alignments of glutaminases and glutamine synthetase genes as submitted in a communication filed on 7/31/2007 is acknowledged.

New claims 20-21 are directed to the elected subject matter. This application contains claims 8-11 drawn to an invention nonelected with traverse in a communication filed on 6/30/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1, 4-5, 12-16, 18-21 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112, Second Paragraph***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 4-5, 13-16, 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

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3. Claims 1, 5, 16 (claims 4, 13-15, 18-21 dependent thereon) are indefinite in the recitation of “95% or more homologous to SEQ ID NO: X” for the following reasons. The term “95% or more homologous to SEQ ID NO: X” is unclear and confusing in the absence of a definition providing the intended meaning of the term or the intended parameters required to determine the required homology value. While one could argue that the term “sequence homology” can be interpreted as “sequence identity”, as known in the art, these terms are not equivalent. The calculation of sequence homology takes into consideration the type of mismatches, i.e. even mismatches contribute to the % homology value, whereas mismatches do not have any weight in the calculation of sequence identity, i.e. only exact matches contribute to the % identity value. Thus, if there is no indication that the term “homology” is intended to mean “identity”, and the specification does not provide the specific parameters intended in the calculation of sequence homology (e.g., PAM matrices), one of skill in the art cannot determine the scope of the term “95% homologous” because one could have a nucleic acid sequence which is 95% sequence homologous to a reference sequence based on a particular matrix/set of parameters, and at the same time, not 95% sequence homologous to the same reference sequence if other matrices/parameters are used. For examination purposes, no patentable weight will be given to the term. Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 4-5, 12-16, 18-19 remain rejected and new claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

6. This rejection has been discussed at length in the Non Final action mailed on 3/5/2007 and it is applied to new claim 21 for the reasons of record and those set forth below.

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7. Applicant argues that claims 1, 5 and 16 have been amended to recite “95% or more”. Also, Applicant submits that the claims have been amended to indicate that the increase in glutamine synthetase activity is achieved by increasing the copy number of the gene or by replacing the endogenous promoter with a strong promoter. Applicant also refers to BLAST search results (Exhibits A and B) for the protein of SEQ ID NO: 2 and the nucleic acid of SEQ ID NO: 3. Applicant argues that based on the alignment provided, one of skill in the art can determine which regions are important for glutaminase activity and would be able to reduce glutaminase activity by introducing mutations at such regions. Furthermore, Applicant contends that one of skill in the art can use information regarding glutaminase genes to determine how to mutate the regulatory region of a glutaminase gene to obtain the desired reduction in glutaminase activity.

8. Applicant’s arguments have been fully considered but are not deemed persuasive to overcome the instant rejection or avoid the rejection of new claim 21. The Examiner acknowledges the amendments made to the claims and the submission of Exhibits A and B. However, the Examiner disagrees with Applicant’s contention that the claims as amended (or new claim 21) are adequately described by the teachings of the specification. The claims as written still require any type of modification in a coryneform bacterium glutaminase gene which would (1) reduce glutaminase activity to levels less than 0.1 U/mg of cellular protein or 0.01 U/mg of cellular protein, and (2) further result in a ratio of glutamine synthetase activity to glutaminase activity of 2 to 1. In addition to the modifications to the glutaminase gene, claims 4 and 15 also require any modification in the coryneform bacterium such that the level of glutamine synthetase activity in the coryneform bacterium is increased to achieve the required ratio (e.g., endogenous glutamine synthetase activity is not sufficient to achieve the 2 to 1 ratio). This encompasses, for example, addition of transcription inducers, mutations in the regulatory region of a glutamine synthetase gene to increase transcription of said gene, transformation of the coryneform bacterium with a vector that expresses any glutamine synthetase gene, etc. While the specification has disclosed a single

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method (inactivating deletion) by which glutaminase activity in *C. glutamicum* can be reduced to the recited levels, the specification is otherwise silent with regard to other modifications/mutations which would allow one of skill in the art to achieve the required glutaminase levels or the required ratio of glutaminase/glutamine synthetase activity. With regard to arguments that structural comparisons would allow one of skill in the art to determine which modifications would result in reduced glutaminase activity, it is noted that neither the specification nor the art provide any teaching or suggestion as to which structural features in any glutaminase gene are associated with controlling transcription levels and how those structural features should be modified such that the recited glutaminase activity levels are achieved. Also, no structure/function correlation has been provided for glutaminases such that one of skill in the art can determine (1) which amino acids in any glutaminase can be modified, and (2) how they should be modified to obtain the recited enzymatic activity levels. At best, alignments using different glutaminases known in the art would provide those regions which appear to be conserved among the glutaminases used in the alignment. The alignment, however, would not provide any indication as to how the conserved regions are related to the activity in question, nor would they provide any indication as to how they should be modified to decrease enzymatic activity to the exact levels recited in the claims. Thus, for the reasons extensively discussed in previous Office actions and those set forth above, one cannot reasonably conclude that the claimed invention is adequately described by the teachings of the specification.

9. Claims 1, 4-5, 12-16, 18-19 remain rejected and new claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *C. glutamicum* cell wherein said cell has been modified to reduce glutaminase activity and to increase glutamine synthetase activity, wherein the reduction in glutaminase activity is due to an inactivating deletion in the *C. glutamicum* glutaminase gene of SEQ ID NO: 1, and the increase in glutaminase activity is due to (i) an increase in the copy number of the *C. glutamicum* glnA gene of SEQ ID NO: 3, or (ii) an increase in

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expression of the *C. glutamicum* glnA gene of SEQ ID NO: 3 by placing said gene under the control of a heterologous promoter, does not reasonably provide enablement for (1) a coryneform bacterium modified to reduce glutaminase activity to less than 0.1 U/mg protein or 0.01 U/mg protein in said bacterium by mutating any region of a glutaminase gene comprising SEQ ID NO: 1 or a structural homolog thereof, (2) the coryneform bacterium of (1) further modified in any way to increase glutamine synthetase activity such that the recited ratio (2 to 1) of glutamine synthetase activity to glutaminase activity is achieved, or (3) the coryneform bacterium of (1) further modified by increasing the expression of a glutamine synthetase gene which is a structural homolog of the nucleic acid of SEQ ID NO: 3, wherein said increase in expression is obtained by increasing the copy number of the glutamine synthetase gene or by replacing the endogenous promoter of the glutamine synthetase gene with a stronger promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

10. This rejection has been discussed at length in the Non Final action mailed on 3/5/2007 and it is applied to new claims 20-21 for the reasons of record and those set forth below.

11. Applicant's arguments are those already been summarized above with regard to written description rejection.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection or avoid the rejection of new claims 20-21. As indicated above, no patentable weight has been given to the term "95% or more...". The amendments and exhibits provided are acknowledged. However, the Examiner disagrees with Applicant's contention that the full scope of the claims is enabled by the teachings of the specification and/or the art. In view of how the claims have been interpreted, the claims still require an extremely large genus of structural homologs of the genes of SEQ ID NO: 1 and 3 which hybridize under the conditions recited to the nucleic acids of SEQ ID NO: 1 and 3. As previously

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discussed in the Non Final action of 3/5/2007, the number of nucleic acids recited is essentially infinite and can encode proteins having almost no structural similarity to the polypeptides of SEQ ID NO: 2 or 4.

In addition, the claims require any type of modification in a coryneform bacterium glutaminase gene which would (1) reduce glutaminase activity to levels less than 0.1 U/mg of cellular protein or 0.01 U/mg of cellular protein, and (2) further result in a ratio of glutamine synthetase activity to glutaminase activity of 2 to 1. As indicated above, claims 4 and 15 also require any modification in the coryneform bacterium such that the level of glutamine synthetase activity in the coryneform bacterium is increased to achieve the required ratio. As such, the claims encompass modifications such as addition of transcription inducers, mutations in the regulatory region of any glutamine synthetase gene to increase transcription of said gene in the coryneform bacterium, and transformation of the coryneform bacterium with a vector that expresses any glutamine synthetase gene. The specification has disclosed a single method (inactivating deletion) by which glutaminase activity in *C. glutamicum* can be reduced to the recited levels. However, the specification fails to provide any teaching or guidance as to other modifications/mutations which would allow one of skill in the art to achieve the required glutaminase levels or the required ratio of glutaminase/glutamine synthetase activity. In view of the fact that no teaching or suggestion has been provided which would allow one of skill in the art to determine which mutations/modifications are more likely to produce the desired enzymatic activity levels, one of skill in the art is left with the task of testing an essentially infinite number of mutations/modifications to enable the full scope of the claims.

Arguments indicating that structural comparisons would allow one of skill in the art to determine the modifications that would result in the recited glutaminase activity levels have been considered but are not deemed persuasive. At best, an alignment using different glutaminases known in the art would provide those regions which appear to be conserved among the glutaminases used in the alignment, but would not provide any indication as to how the conserved regions are related to the activity in question, nor would they provide any indication as to how they should be modified to decrease enzymatic activity



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to the exact levels recited in the claims. Moreover, neither the specification nor the art provide any teaching or suggestion as to which structural features in any glutaminase gene (or the *C. glutamicum* glutaminase gene) are associated with modulating transcription levels and how those structural features should be modified such that the recited glutaminase activity levels are achieved. Also, no structure/function correlation has been provided for glutaminases such that one of skill in the art can determine a priori (1) which amino acids in any glutaminase can be modified, and (2) how they should be modified to obtain the recited enzymatic activity levels. As extensively discussed in previous Office actions, the art teaches how even small structural changes can affect function. It is reiterated herein that in view of the lack of information provided, the amount of experimentation required to enable the entire scope of the claims is undue as it would require testing an extremely large number of nucleic acid variants and determine, for example, (1) which ones encode glutaminases, (2) which of the glutaminases of (1) have the recited levels of enzymatic activity, (3) which ones encode glutamine synthetases, (4) which of the glutamine synthetases of (3) have the recited levels of enzymatic activity, (5) which ones would be overexpressed as a result of a modification in the regulatory region, and (6) which ones would be expressed in low amounts such that the enzymatic levels recited are achieved. Thus, for the reasons extensively discussed in previous Office actions and those set forth above, one cannot reasonably conclude that the claimed invention is fully enabled by the teachings of the specification.

***Claim Rejections - 35 USC § 103***

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. Claims 1, 4-5, 7, 13-16, 19 remain rejected and new claims 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura et al. (EP 1229121 A2 published 8/7/2002; cited in the IDS) in view of Pompejus et al. (WO 01/00843, published 1/4/2001; cited in the IDS) and further in view of

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Duran et al. (Microbiology 141:2883-2889, 1995). This rejection has been discussed at length in previous Office actions and it is applied to new claims 20-21 for the reasons of record and those set forth below.

15. Applicant argues that the strain of Duran et al. is not a glutamine-producing strain because the strain of Duran et al., when grown in the presence of succinate and glutamine, displays intracellular levels of glutamine which are lower than when the strain is grown solely in the presence of glutamine.

Applicant submits that the strain of Duran et al. is known to have an additional enzyme (called GOGAT by Applicant; known in the art as glutamate synthetase) which can also degrade glutamine in the presence of  $\alpha$ -ketoglutarate. Applicant suggests that the reason why Duran et al. observed an accumulation of glutamine was not due to the inactivation of the glutaminase gene but due to the low levels of  $\alpha$ -ketoglutarate, which did not allow GOGAT to degrade glutamine. Applicant argues that when succinate was added, less glutamine was accumulated, probably because the addition of succinate allowed for the formation of  $\alpha$ -ketoglutarate, which in turn allowed GOGAT to degrade glutamine. Applicant speculates that if glucose would have been added to the medium, GOGAT would have degraded glutamine even more. Applicant concludes that the teachings of Duran et al. do not teach or suggest that an increase in glutamine levels in a glutaminase-deficient strain when glucose is present in the medium. With regard to Nakamura et al., Applicant submits that Nakamura et al. teach glutamine fermentation by a coryneform bacterium in the presence of glucose and does not teach disabling the glutaminase gene. With regard to Pompejus et al., while not disputing the fact that this reference teaches the glutaminase and glutamine synthetase genes from *C. glutamicum*, Applicant submits that there is no reason for one of skill in the art to combine the teachings of these references.

16. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection or avoid the rejection of new claims 20-21. New claims 20-21 are directed in part to the bacterium of claim 1 with the added limitation that the glutaminase gene in the chromosome has been

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disrupted. It is noted that mutating a gene on the chromosome can encompass disrupting that gene via a deletion in that gene. Also, due to the fact that the Examiner has not given any patentable weight to the term “95% or more homologous to SEQ ID NO: X” for the reasons extensively discussed above in Claim Rejections under 35 USC 112, second paragraph, the nucleic acids of Pompejus et al. meet the hybridization limitations recited.

The Examiner acknowledges that the degradation of glutamine is not carried out only by glutaminase. Clearly, glutamate synthetase would also use glutamine as a substrate. However, even if one takes into account the possibility of other enzymes also degrading glutamine, this fact would not lead one of skill in the art to conclude that it is unlikely that inactivating glutaminase would not result in some reduction in glutamine degradation. While Duran et al. teach that growth substrate is a factor in how much glutamine accumulation is obtained, even when peptone+yeast extract was used, Duran et al. observed twice the amount of intracellular glutamine compared to the wild type strain (Table 1, last entry). If the objective is to produce glutamine, the results of Duran et al. would not only provide motivation to create a coryneform bacterium which is glutaminase-deficient for enhanced glutamine production, but would also provide the skilled artisan with a reasonable expectation of some glutamine accumulation as a result of inactivating glutaminase.

The Examiner disagrees with Applicant's contention that Duran et al. teach away of using a glutaminase-deficient strain for accumulation of glutamine if the strain is grown in the presence of glucose, in view of the fact that (1) there is no teaching or suggestion in Duran et al. indicating that no glutamine accumulation is expected in the presence of glucose, and (2) there is no experimental evidence by Applicant or the prior art showing that the strain of Duran et al., when grown in the presence of glucose, would provide absolutely no glutamine accumulation. Even if it is assumed that the contribution of GOGAT in glutamine degradation would be higher if the strain is grown in glucose, it is unlikely that the lack of glutaminase activity would have no effect whatsoever on glutamine levels. The teachings of

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Duran et al. clearly suggest that there is an effect on glutamine levels when glutaminase is inactivated. Therefore, the teachings of the art, as evidenced by Duran et al., make the inactivation of glutaminase not only obvious to try but also provide a reasonable expectation of observing some glutamine accumulation.

With regard to arguments that Duran et al. do not teach an L-glutamine producing organism, it is noted that while it is acknowledged that the strain of Duran et al. is not considered a high L-glutamine producer such as the *C. glutamicum* strain taught by Nakamura et al., it meets the definition given in the specification for an L-glutamine producing organism in view of the fact that this bacterium will produce L-glutamine and some L-glutamine will accumulate in the growth medium partly due to cell lysis. It should be noted that the definition provided in the specification does not place any limitations on how much L-glutamine has to accumulate in the medium for the organism to be considered an L-glutamine producer. However, as indicated in previous Office action, the Examiner has relied on the teachings of Nakamura et al. for meeting the limitation “coryneform bacterium having L-glutamine-producing ability” required by the claims.

With regard to the teachings of Nakamura et al., it is noted that Nakamura et al. do not teach glucose-containing media as the only media in which coryneform bacteria can be grown, nor does it teach away from growing *C. glutamicum* in media that do not contain glucose. Also, while it is acknowledged that Nakamura et al. do not teach inactivation of the glutaminase gene, this limitation is clearly suggested by the teachings of Duran et al. previously discussed. Thus, contrary to Applicant’s assertions, there is not only a clear motivation but a reasonable expectation of success in combining the teachings of Nakamura et al., Duran et al., and Pompejus et al. As such, the claimed invention is deemed obvious over the cited prior art.

### ***Conclusion***

17. No claim is in condition for allowance.

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18. As indicated above, this action is identical to that submitted to Applicant on 10/16/2007 except for the addition of claim 12 in the list of claims rejected under 35 USC 112, first paragraph. As indicated in that action, Applicant's amendment filed on 7/31/2007 necessitated the new ground(s) of rejection presented in the Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.  
Primary Patent Examiner  
Art Unit 1652

DR  
March 19, 2008